REMARKS

Following entry of the foregoing amendments, claims 1, 4 to 6, 9, 21, 24, 25, 36, 37, and 101 will be pending in this patent application. Claims 1, 4 to 6, 9, 21, 24, 25, 36, and 37, have been amended, and claims 10 to 13 been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed, including, for example, paragraphs 75, 275, and 276. The amendments thus do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

Claims 1, 4 to 6, 9 to 13, 17, 21, 24, 25, 36, 37, and 101 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by U.S. patent application publication number US 2004/0259247 ("the Tuschl application") in view of Schwarz, *et al.*, *Molecular Cell*, 2002, 10, 537-548 ("the Schwarz article"), Manoharan *et al.*, *Tetrahedron Letter*, 1995, 36, 3651-3654 ("the Manoharan article"), and Crooke, S.T., ed., Marcel Dekker, New York 2001, Chpt. 16, 391-467 ("the Crooke chapter").[1] If the Office considers this rejection to apply to the claims as amended herein, applicants respectfully request reconsideration and withdrawal thereof because the cited references fail to describe or suggest the presently claimed compositions that comprise a complementary pair of first and second oligomeric compounds in which the first (antisense) oligomeric compound comprises a steroid attached to the 3'-terminal monomeric subunit of the oligomeric compound, and the second (sense) oligomeric compound comprises a steroid attached to the 5'-terminal monomeric subunit of the oligomeric compound.

Specifically, the Tuschl application contains no teaching or suggestion whatsoever of conjugation of steroids to the ends of double-stranded siRNA molecules. Instead, the Tuschl application describes double-stranded RNA molecules that mediate target-specific RNA

[1] Applicants assume that citation of the Crooke chapter was an inadvertent error because it is not discussed at any point in the official action, and therefore apparently does not actually serve as a basis for the rejection for alleged obviousness. The teachings of the reference are therefore not discussed by applicants.

interference or other target-specific nucleic acid modifications, such as DNA methylation.[2] The Tuschl application states that the RNA molecules may contain at least one modified nucleotide analogue and indicates that possible modifications include sugar, backbone, and nucleobase modifications.[3] The Tuschl application fails to describe or suggest, however, modifying the duplex RNAs by attachment of conjugate moieties, much less steroids, to the 3'-terminal monomeric subunit of the antisense strand and the 5'-terminal monomeric subunit of the sense strand, as claimed. The Tushcl application therefore fails to provide any reason that would have prompted those skilled in the art to produce duplexes having such conjugates before applicants' invention.

The Schwarz article similarly fails to describe or suggest duplexes of oligomeric compounds having steroids conjugated to each strand, and the combination of the Schwarz and Tushcl articles thus fails to describe or suggest the presently claimed duplexes. In this regard, the Schwarz article describes experiments demonstrating that attachment of a methoxy group to the 5' end of the guide (or antisense) strand of siRNA molecules abolishes the RNAi activity of the molecules. Significantly, the Schwarz article describes attachment of a relatively small entity, a methoxy group, to the 5' end of the guide strand, and does not describe or suggest conjugation of much larger groups, such as steroids, to the 5' end of the guide strand, or to any position in an siRNA molecule for that matter. Accordingly, the Schwarz article provides no indication as to what effects attachment of relatively large molecules, such as steroids, would have on RNAi activity when conjugated to the 5' end of the guide strand of siRNAs, much less the effect that conjugation of steroids to both the 3' end of the guide strand and the 5' of the sense strand would have. The Schwarz article thus fails to describe or suggest the claimed duplexes, and also provides no teaching that would have prompted those skilled in the art to produce such duplexes due to the lack of any indication that such molecules would be active in RNAi.

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[2] Paragraph 8.
[3] Paragraphs 15 to 16.

Finally, the Manoharan article fails to supply the missing teachings and suggestions of the Tuschl application and the Schwarz article. The combination of the three references thus fails to describe or suggest the claimed duplexes, and also fails to provide any reason that would have prompted those skilled in the art to produce such duplexes. Instead, the Manoharan article describes the incorporation of lipid-conjugated nucleosides into single-stranded antisense DNA oligonucleotides, which exert their biological activity by serving as substrates for RNase H. Significantly, the Manoharan article contains no teaching or suggestion of conjugation of lipids to siRNA molecules, much less conjugation of steroids to both the 5' end of the sense strand and the 3' end of the antisense strand of siRNAs, and accordingly provides no indication as to the effect that such conjugates would have on the resulting duplexes. Accordingly, based upon the description provided in the Manoharan article, those skilled in the art would have had no reason to prepare duplexes of oligomeric compounds in which a steroid is attached to a 3'-terminal monomeric subunit of the antisense strand of the duplex and the 5'-terminal monomeric subunit of the sense strand, as claimed.

When considering the combined teachings of the cited references, those of ordinary skill in the art therefore would have had no reason to design and produce the claimed complementary pairs of oligomeric compounds in which a steroid is conjugated to the 3' end of the first ansisense oligomeric compound and a steroid is conjugated to the 5' end of the second sense oligomeric compound, due to the lack of any teaching or suggestion of such molecules in the references, and due to the further lack of any indication in the references that such molecules would be active in RNAi or would have any beneficial or desirable properties or characteristics. Compositions comprising such oligomeric compounds therefore would not have been obvious at the time of the invention. (A finding of obviousness requires the Office to identify "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the [known] elements *in the way the claimed new invention does*."[4] Moreover, "it remains necessary to identify some *reason* that would have led a chemist to modify a known compound in a particular

[4] *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727 (2007) (emphasis added).

manner to establish prima facie obviousness of a new claimed compound."[5]) Applicants accordingly, respectfully, request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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[5] *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added).